REMARKS

Claims 1-6, 11 and 12 are all the claims pending in the application. Claim 13 is canceled. Claim 2 is withdrawn as being directed to a non-elected species.

Claims 6, 11, and 12 have been amended to depend from claims 1 and 3-5, in view of the withdrawal of claim 2. Claim 6 has further been amended to recite a pharmaceutically acceptable carrier to distinguish the scope from that of claims 1 and 3-5. Support is found at least at page 25 lines 7-17. Claims 11 and 12 are also amended to delete prevention of conditions, to replace "those" with "said" and to delete various members of a Markush group. Support for reciting muscle wasting disease in claim 11 is found at least at page 24, lines 14-17.

No new matter is added.

A. Information Disclosure Statements

The Examiner has not returned the PTO Form SB/08 that accompanied the Submission of International Search Report filed December 17, 2004, possibly because copies of the references were not submitted or transmitted by the International Bureau. Accordingly, submitted herewith are copies of the references cited with the Submission of International Search Report. The Examiner is requested to consider the references and return the PTO Form SB/08 signed and initialed.

B. Election/Restrictions

The Examiner acknowledges Applicant's election with traverse of Group IV with the selection of substituent Z as heteroaryl.

The Examiner is thanked for rejoining amended claim 6, drawn to a composition of the elected Group IV compounds and a pharmaceutically acceptable carrier or excipient, and claims 11 through 13 drawn to methods of prevention and treatment with same compounds.

With respect to the Restriction into Groups I-IX based upon the compound defined, the Examiner asserts that the Restriction is correct because the claims of this National Stage Application are not so linked as to form a single general inventive concept under PCT Rule 13.1. Specifically, the Examiner states that the single general inventive concept shared by Groups I through IX is that the compounds are all tetrahydroquinoline derivatives. However, the Examiner states that the tetrahydroquinoline derivatives are not novel, citing Hayes et al. and another reference.

According to the Examiner, Hayes et al. teach a tetrahydroquinoline derivative wherein with respect to the instant formula (I) R^1=NO_2 or CN, R^2=H, X=CH, m=0 and the Y-N(R^9)[(CO)Z] equivalent is C_2-C_{10} substituted alkyl. (See Hayes et al, US 5,925,527, 20 July 1999, columns 3 and 4.)

While Applicant does not further traverse this Restriction Requirement, Applicant submits that the Examiner's understating of Hayes et al. (U.S. Patent No. 5,925,527) is incorrect. The compounds of Formula I disclosed in Hayes et al. have Y-R^1- as a substituent of the tetrahydroquinoline moiety wherein Y is CO_2H, OH, SH, NHR^7, $C(O)NHR^7$, CH_2OH, CH_2NH_2 or CH_2NHR^7. Therefore, Hayes et al. do not disclose the tetrahydroquinoline moiety substituted only by CN or NO_2.

C. Obviousness-type double patenting

Claims 1 and 3 through 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/522,553 (US 2005/0277660) in view of Hanada et al., (US 7,037,919).

This rejection is overcome by the submission of a Terminal Disclaimer.

D. Claim rejections - 35 U.S.C. § 112, first paragraph (enablement)

Method claims 11 through 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of androgen receptor-linked bone tissue conditions, allegedly does not reasonably provide enablement for the "prevention" of any disease or for the treatment of all androgen receptor-linked diseases.

The claims have been amended to remove recitation of prevention of conditions.

With respect to treatment of all androgen receptor-linked diseases, the Examiner states that lack of enablement is clearly indicated in the instant disclosure on page 4, lines 6 and 10 which states that "..globally recognized compounds are yet to be created" and "..no such compounds are yet to be created". The Examiner states that this statement demonstrates clearly that the mechanism is by no means definite if the compounds affecting androgen receptor-linked diseases are not yet known.

The Examiner also asserts that literature (or the lack thereof) within the relevant art also supports this uncertainty, as only a single reference is cited in support of a quinoline derivative (a quinolin-2-one) having anabolic effects on bone and muscle, as well as activity in a sexual behavior model. The Examiner asserts that Miner et al make reference to possible quinoline

derivative activity stating "..nonsteroidal selective androgen receptor modulators may be useful therapeutics for enhancing muscle, bone, and sexual function," and that this statement demonstrates clearly that the mechanism is by no means definite, and that further research effort would be needed to establish and confirm the treatments.

Accordingly, the Examiner concludes that the amount of experimentation needed to confirm and clearly establish the compounds of formula (I) as treatments for all the androgen receptor-linked conditions listed in claims 12 and 13 is considerable. The Examiner asserts that the working examples in the specification are consistent with this position in that the working examples stop at the androgen receptor binding activity, and fail to establish the desired link between androgen receptor activity and all the diseases of the disclosure.

With respect to treatment of androgen receptor linked diseases, the claims have been amended to recite osteoporosis, muscle wasting and male hypogonadism. These androgen receptor-linked conditions are clearly supported by the working examples in the specification.

Applicant further submits that the Examiner has misunderstood the disclosure of the present specification. That is, "... no such compounds are yet to be created ..." on page 4, lines 6 to 10 means -- no small molecular compounds as the present invention have been found --. The compounds affecting androgen receptor-linked diseases were also known in steroid compounds and the mechanism was also known, as is clear from Chapter 19 of the text book "Androgen Replacement Therapy of Male Hypogonadism". (copy submitted herewith) Also, Miner et al. only refer to nonsteroidal compounds. Therefore, it cannot be said from the disclosure of Miner et al. that the mechanism of the compounds affecting androgen receptor-linked diseases is indefinite.

E. Claim rejections - 35 U.S.C. § 112, second paragraph

Claims 11 through 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

1. Claims 11 through 13 recite the phrase "treat those diseases" which allegedly renders the claims indefinite because it is unclear whether the limitations preceding the phrase are part of the claimed invention. The Examiner asserts that "those" is a term generally used for counter distinction contrasting with something currently applicable or near. The Examiner suggests Applicant use more standard terms such as "treat said diseases".

To further clarify the claimed invention, the Examiner's suggestion to replace "those" with "said" has been adopted.

2. Claim 11, drawn to a method of preventing or treating wasting disease or osteoporosis, is rejected based on the lack of clarity with respect to "wasting disease". The Examiner recognizes that the disclosure indicates a group of conditions as "wasting diseases", however claim 11 is drawn to treating "wasting disease" in the singular. The Examiner asserts that the claim should appropriately specify the specific conditions that constitute the wasting diseases for which treatment is enabled.

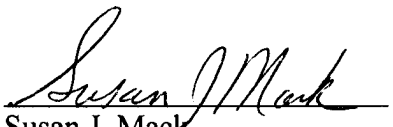
The claim has been further clarified by replacing the term "wasting disease" with the phrase "muscle wasting."

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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19 Androgen Replacement Therapy of Male Hypogonadism

A. Wayne Meikle, MD

Contents

INTRODUCTION

Male hypogonadism is a relatively common disorder in clinical practice, particularly in aging men, and has significant effects on the fertility, sexual function, and general health of patients *(1–8)*. Disorders of sperm and testosterone (T) production may be caused by primary, secondary, or tertiary hypogonadism. Some are relatively common and others are rare *(9–11)*. In aging men, a tertiary-like deficiency leads to T deficiency, which affects about 20% of men by age 60 yr *(5,12–14)*. In men with clinical manifestations of primary or secondary hypogonadism, deficiency of T can usually be treated effectively. Fertility in some men with primary testicular disease, such as Klinefelter's syndrome, is irreversible, but those with gonadotropin deficiency resulting in infertility can often be treated successfully (as reviewed in Chapter 24) *(15–17)*. Although both T deficiency and infertility can be corrected using gonadotropin or gonadotropin-releasing hormone (GnRH) therapy in men with hypogonadotropic hypogonadism, this form of therapy is usually restricted to the management of infertility. Otherwise, androgen-replacement therapy is used to correct the chronic T deficiency. Thus, knowledge of the pathophysiology of hypogonadism is needed to plan and use appropriate hormonal replacement therapy in men with deficiency of T and sperm production.

This chapter will focus primarily on androgen-replacement therapy for T deficiency. Androgen-replacement therapy with injectable, oral, and (more recently) transdermal

From: *Endocrine Replacement Therapy in Clinical Practice*
Edited by: A. Wayne Meikle © Humana Press Inc., Totowa, NJ

and injectable pellets preparations has been available to physicians for years. However, an orally active preparation with reliable efficacy may contribute to more widespread acceptance and use of T therapy by many men.

OVERVIEW OF PHYSIOLOGY OF THE TESTES

Pulsatile secretion of GnRH by the hypothalamus stimulates the release of gonadotropins (luteinizing [LH] and follicle-stimulating hormone [FSH]) *(1,8)*. LH stimulates Leydig cells to synthesis and secrete T, which has feedback effects on LH secretion. The seminiferous tubule compartment comprising about 85% of the mass of the testes contains Sertoli cells, which surround developing germ cells that produces mature spermatozoa. FSH binds to receptors on Sertoli cells and stimulates them to produce an androgen-binding protein, enabling the testes to concentrate T many-fold above the serum levels. Inhibin made by Sertoli cells has a feedback influence on FSH secretion *(17–21)*.

Testosterone and its potent 5-α reduced metabolite, dihydroT (DHT), have important physiologic influences during embryogenesis, puberty, and adulthood *(8)*. During fetal development, T and DHT result in normal differentiation of male internal and external genitalia *(22,23)*.

During puberty, T and DHT are required for the development and maintenance of male secondary sexual characteristics. DHT results in growth of the prostate and masculinization of the skin *(8,24)*, and the remaining androgen effects are from the actions of T. In adults, T and DHT are required for the maintenance of libido and potency, muscle mass and strength, fat distribution, bone mass, erythropoiesis, prostate growth, male pattern hair growth, and spermatogenesis.

Pathophysiology of Hypogonadism

Hypogonadism is caused by disorders of the testes (primary, as listed in Table 1), pituitary (secondary), or hypothalamus (tertiary) *(1,8)*. T deficiency may occur as the result of Leydig cell dysfunction from primary disease of the testes, inadequate LH secretion from diseases of the pituitary, or impaired GnRH secretion by the hypothalamus. Pinpointing the cause and extent of hypogonadism makes it possible to tailor successful replacement therapy (*see* Table 2). Men with primary gonadal failure usually have either isolated azoospermia or oligospermia or azoospermia and T deficiency. T therapy is offered to men with androgen deficiency when successful fertility is improbable or not desired.

General Manifestations

Clinical Presentation

The clinical presentation of male hypogonadism depends on the stage of sexual development *(1,8)*. Androgen deficiency occurring during fetal development from defects in androgen synthesis, metabolism, or androgen responsiveness results in various manifestations of male pseudohermaphroditism.

Prepubertal. In boys with prepubertal hypogonadism, expression of the androgen deficiency is seldom recognized before the typical age for onset of puberty except in those with associated growth retardation or other anatomic and endocrine abnormalities. Failure of puberty is well characterized by several clinical features, as shown in Table 3.

Table 1
Causes of Hypogonadism

- Gonadal defects
  - Genetic Defect-Klinefelter's syndrome, myotonic dystrophy, Prader–Willi syndrome
  - Polyglandular autoimmune failure syndromes (e.g., Schmidt syndrome)
  - Anatomic defects
  - Toxins: cytotoxic agents, spironolactone, alcohol
  - Radiation
  - Orchitis: usually as a result of mumps
- Hormone resistance
  - Androgen insensitivity
  - Luteinizing hormone insensitivity
- Hypopituitarism
  - Idiopathic
  - Tumor
  - Other causes
- Hyperprolactinemia
  - Usually the result of pituitary adenoma
  - Idiopathic increased prolactin production
- Gonadotropin deficiency
  - Hypogonadotropic hypogonadism
  - Isolated congenital idiopathic GnRH deficiency
    - GnRH deficiency with anosmia: Kallman syndrome
    - Acquired GnRH deficiency is very uncommon
  - Respond to pulsatile GnRH administration
  - Hypothalamic insufficiency
  - LH or FSH deficiency
- Systemic diseases
  - Chronic diseases
  - Malnutrition/starvation
  - Massive obesity
  - AIDS/HIV

Table 2
Laboratory Testing of Hypogonadism

Hypothalamic	*Primary hypogonadism*	*Seminiferous tubule disease*	*Leydig cell failure*	*Pituitary disease*	*Hypothalamic disease*
T	Low	Normal	Low	Low	Low
LH	High	Normal	High	Low	Low
FSH	High	High	Normal	Low	Low
Sperm count	Low	Low	Low	Low	Low
LH and FSH response to GnRH	Normal	Not done	Not done	Low	Normal

Review: Interpreting the results (1)T low, LH and FSH elevated → primary hypogonadism; order karyotype. (2) T low, LH and FSH normal or low → secondary hypogonadism, obtain PRL and computed tomography scan of head to screen for mass lesion; remaining pituitary hormones must be tested for deficiency. (3) T and LH normal, FSH high → abnormal seminiferous tubule compartment; order semen analysis. (4) T, LH and FSH high → androgen resistance syndrome.

Table 3
Clinical Presentation of Peripubertal Hypogonadism

Small testes, phallus, and prostate (prepubertal testes are between 3 and 4 mL in volume and less than 3 cm long by 2 cm wide; peripubertal testes are between 4 and 15 mL in volume and 3–4 cm long by 2–3 cm wide)
Lack of male-pattern hair growth
Scant pubic and axillary hair, if adrenal androgens are also deficient
Disproportionately long arms and legs (from delayed epiphyseal closure, eunuchoidism; with the crown-to-pubis ratio <1 and an arm span more than 6 cm greater than height)
No pubertal growth spurt
No increase in libido or potency
Reduced male musculature
Gynecomastia
Persistently high-pitched voice

Table 4
Clinical Presentation of Postpubertal Hypogonadism

Progressive decrease in muscle mass
Loss of libido
Impotence
Infertility with oligospermia or azoospermia
Hot flashes (with acute onset of hypogonadism)
Osteoporosis
Anemia
Adult testes are usually between 15 and 30 mL and 4.5–5.5 cm long by 2.8–3.3 cm wide
Mild depression
Reduced energy

Postpubertal. Postpubertal loss of testicular function may be manifested by infertility and androgen deficiency. The clinical symptoms and signs may evolve slowly, making them relatively subtle, particularly in older men in whom they are incorrectly attributed to aging. The growth of male pattern body hair often slows, but the change of the voice and the size of the phallus, testes, and prostate may be undetectable. In younger men, a delay in temporal hair recession and balding may go unnoticed as a manifestation of T deficiency. Men with postpubertal hypogonadism may have some or all of these clinical findings, as summarized in Table 4.

GOAL OF ANDROGEN THERAPY

In androgen-replacement therapy, a safe, general principle is to mimic the normal concentrations of T (350–1050 ng/dL) and its active metabolites *(25–29)*, thereby avoiding unphysiologically high or low serum T concentrations. (Clearly, patients experience symptoms with androgen deficiency, but whether unphysiologically high concentrations carry health risks is unknown.) When these goals are met, physiological responses to androgen-replacement therapy allows virilization in prepubertal males and restoration or preservation of virilization in postpubertal men. The therapy should not have

untoward health hazards on the prostate, serum lipids, and cardiovascular, liver and lung function. Ideally, therapy should allow self-administration, be convenient, cause minimal discomfort, and result in reproducible daily pharmacokinetics at a reasonable cost. None of the currently available androgen-replacement therapies achieves the ideal, but their relative merits will be discussed. A review will be made comparing the pharmacokinetics of different androgen preparations widely used for substitution therapy.

OVERVIEW OF PHARMACOLOGY OF ANDROGENS

Historical Aspects

Evidence that the testes produced virilizing substances initially was observed by Berthold in 1849 *(30)*, who transplanted testes from roosters into the abdomen of capons, which made them behave like normal roosters. Butenandt in 1931 *(31)* was the first to obtain T from urine, and David in 1935 *(32)* crystallized it from the urine of bulls. T was then chemically synthesized by Butenandt and Hanisch in 1935 *(33)* and Ruzick and Wettstein in 1935 *(34)*. After its synthesis, T was introduced for treatment of T deficiency. Because oral pure T was ineffective, subcutaneous T pellets were implanted or T's methyl derivative (methylT) was administered orally. In the 1950s, T ester injections gained widespread acceptance *(35)*. Other derivatives were prepared in an attempt to prepare steroids with anabolic properties. In the 1970s T undecanoate, an oral preparation, became available for clinical use in some countries. Because derivatives of T but not fatty acid esters have hepatic toxicity, the emphasis has recently been on delivering pure T by oral, injectable, or transdermal preparations. Although T is metabolized to potent metabolites by steroid 5-α-reductase to form DHT and aromatase to form estradiol, chemical modification of T results in compounds that are poor substrates for these enzymes.

Oral Testosterone Preparations

Pure Testosterone

Unesterified pure T administered orally is rapidly metabolized by the liver to inactive products and is therefore an ineffective route of administration *(36–39)*.

17α-MethylT

17α-MethylT was the first orally active, synthesized derivative of T (Table 6). After oral administration, peak blood levels are achieved between 1.5 and 2 h, and its serum half-life is about 150 min, suggesting that several doses daily would be required to maintain a therapeutic level of the steroid *(40)*. Hepatic toxicity, including cholestasis, peliosis, elevation of liver enzymes, and reduction of HDL cholesterol limit its use *(41–44)*.

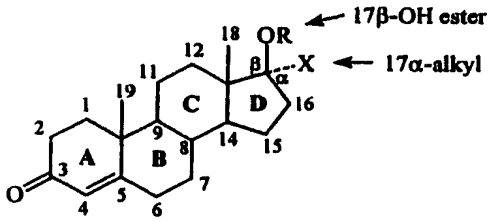
Fluoxymesterone

This steroid is a 17α-methylT steroid with fluorine in the 9 position and has a longer half-life in serum than the parent steroid, but its risk of hepatoxicity limits its clinical use *(41,45–47)*.

Mesterolone

Mesterolone is a derivative of 5 α-dihydrotestosterone with a methyl group in the 1 position. It is not hepatoxic, but it is not metabolized to estrogen, and dosing is difficult to monitor, making it unsatisfactory for replacement therapy *(35,48–53)*.

Table 6
Structure of Testosterone and Its Derivatives



Generic name	*R*	*X*	*Other modifications*
Natural androgens			
Testosterone	H	H	
5α-DihydroT	H	H	4,5-ane
Unmodified 17α esters			
T propionate	$COCH_2CH_3$	H	
T enanthate	$CO(CH_2)_5CH_3$	H	
T cypionate		H	
T undecanoate	$CO(CH_2)_8CH_2{=}CH_2$	H	
Modified 17α esters			
Methenolone acetate	$COCH_3$	H	1-CH_3; 1,2-ene; 4,5-ane
Nandrolone phenylpropionate		H	19-nor CH_3
Nandrolone decanoate	$CO(CH_2)_6CH_3$	H	19-nor CH_3
17α-Alkylation			
MethylT	H	CH_3	
Fluoxymesterone	H	CH_3	9-F; 11-OH
Methandrostenolone	H	CH_3	1,2-ene
Oxandrolone	H	CH_3	C_2 replaced by O; 4,5-ane
Oxymethelone	H	CH_3	2=CHOH; 4,5-ane
Stanozolol	H	CH_3	4,5-ane; {3,2-c}pyrazole
Danazole	H	CH_1CH	{2,3-d}isoxazole
Norethandrolone	H	CH_2CH_3	19-nor CH_3
Ethylestrenole	H	CH_2CH_3	19-nor CH_3; 3-H
Modified androgen			
Mesterolone	H	H	1-CH_3; 4,5-ane

Testosterone Undecanoate

Adding a 17β long aliphatic side-chain ester to T results in good absorption from the gut and substantial uptake by the lymphatics rather than the hepatic portal system. Consequently, free T enters the systemic circulation (63%) without substantial hepatic transformation, and therapeutic T levels are achieved over the first few hours of administration *(29,54–64)*. This preparation is not currently available in the United States, but an improved formulation now being tested in the United States may overcome some of these deficiencies and make it a more satisfactory preparation for androgen replacement therapy.

Sublingual

Sublingual administration of T complexed with hydroxypropyl-β-cyclodextrin results in a rapid rise in serum T, but adequate serum levels of T are sustained for less than 2 h. Its short serum half-life and bitter taste limit its acceptability *(65–68)*.

Testosterone Cyclodextrin

A sublingual preparation contains natural T surrounded by a carbohydrate ring (2-hydroxypropyl-β cyclodextrin), a facilitator of absorption of T through the oral mucosa *(65–69)*. This preparation may produce physiologic levels of T without untoward toxicity, but reproducible manufacture of the preparation has limited further clinical study.

Intramuscular Preparations

Testosterone Esters Overview

Esterification of T at the 17 position with a fatty acid prolongs the intramuscular retention and duration of activity of T in proportion to the length of the fatty acid. When administered intramuscularly *(70)*, the androgen ester is slowly absorbed into the circulation where it is then rapidly metabolized to active unesterified T *(71)*. Intrinsic potency, bioavailability, and rate of clearance from the circulation are determinants of the biological actions of androgens.

Testosterone propionate has a short release phase of only 2–3 d and should not be used for long-term replacement therapy *(72)*. Longer-acting preparations include T enanthate (TE), cypionate (TC) and cyclohexane carboxylate, which all have similar steroid release profiles when injected intramuscularly (*see* Fig. 1). A satisfactory regimen is to administer 200 mg of either T enanthate or cypionate once every 2 wk intramuscularly or 100 mg weekly *(72–76)*. T-*trans*-4-*n*-butylcyclohexyl-carboxylate and T undecanoate are even longer-acting preparations. Blood levels following T-*trans*-4-*n*-butylcyclohexyl-carboxylate administration are sustained for about 12 wk after a large injection of 600 mg in a volume of 2.4 mL *(77)*.

Nandrolone Phenylpropionate and Decanoate

Nandrolone phenylpropionate and decanoate are 17β-hydroxyl esters of 19-norT *(78,79)*, have prolonged action when injected, and are used to treat refractory anemias primarily rather than for androgen-replacement therapy.

Multiple-Dose Pharmacokinetics

As summarized in Fig. 2 and based on simulation and dosing pharmacokinetics, injections of T enanthate (200–250 mg injected every 2 wk) result in a maximal supraphysiological T serum concentrations as high as 51 nmol/L shortly after injection and T serum levels at the lower range of normal T serum concentration (12 nmol/L) before 2 wk *(74,80,81)*.

Testosterone Ester Combinations

Although the intermediate-acting preparations provide high concentrations of T within hours after their administration (*see* Table 5), no advantage has been shown for combining a short- and an intermediate-acting preparation *(74)*.

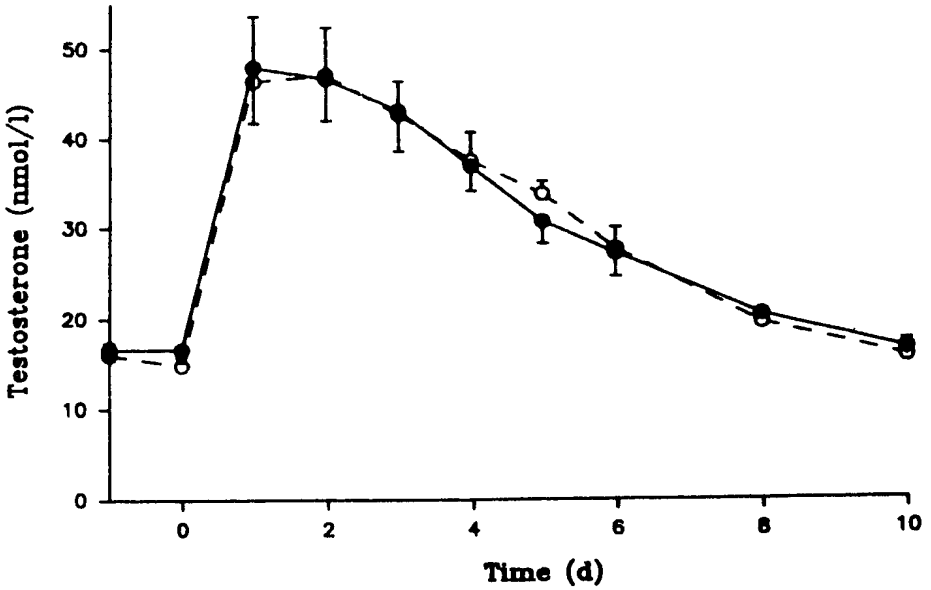


Fig. 1. Comparative pharmacokinetics of 194 mg of T enanthate and 200 mg of T cypionate after intramuscular injection to six normal volunteers. Filled circles: mean ± SEM of T enanthate kinetics; open circles: mean ± SEM of T cypionate kinetics. (From ref. *74*.)

Testosterone Buccilate

Intramuscular injection of 600 mg of T buccilate to hypogonadal men produced serum T concentrations within the normal range for about 8 wk with a terminal elimination half-life of 29.5 d *(77)*. Serum DHT concentrations were within the normal range; estradiol was only slightly increased above normal; SHBG did not change; and gonadotropins were significantly suppressed. No adverse biochemical or prostate responses were reported. It is unknown if this preparation will find use for male contraceptive therapy or replacement for hypogonadism.

Testoserone Undecanoate

Intramuscular injections of 500 and 1000 mg of testosterone undecanoate (TU) in hypogonadal men resulted in increased mean serum T levels from less than 10 nmol/L to 47.8 ± 10.1 and 54.2 ± 4.8 nmol/L, respectively, after about 1 wk. Thereafter, serum T levels decreased progressively and reached the lower-normal limit for adult men by d 50–60 and had a terminal elimination half-life of 18.3 ± 2.3 and 23.7 ± 2.7 d, respectively *(82,83)*. Estradiol and DHT followed the pattern of T and remained within normal limits. In these short-term studies, no serious side effects were noted. Intramuscular TU appears to be well suited for long-term substitution therapy in hypogonadism and hormonal male contraception *(82,83)*.

Subcutaneous Testosterone Implants

Fused pellets or silastic capsules of pure T implanted subcutaneously release T in sufficient quantities to maintain physiologic concentrations of T for between 4 and 6 mo *(84,85)*. The bioavailability of T from subdermal pellet implants approaches 100% by 6 mo (*see* Fig. 3) and is proportional to the dose administered. T pellets implanted in 43 hypogonadal men (6 × 100 mg, 3 × 200 mg, 6 × 200 mg; total of 111 implants) reproducibly maintained serum T concentrations within the normal range for 4–6 mo (*see* Fig. 3) *(84,85)*.

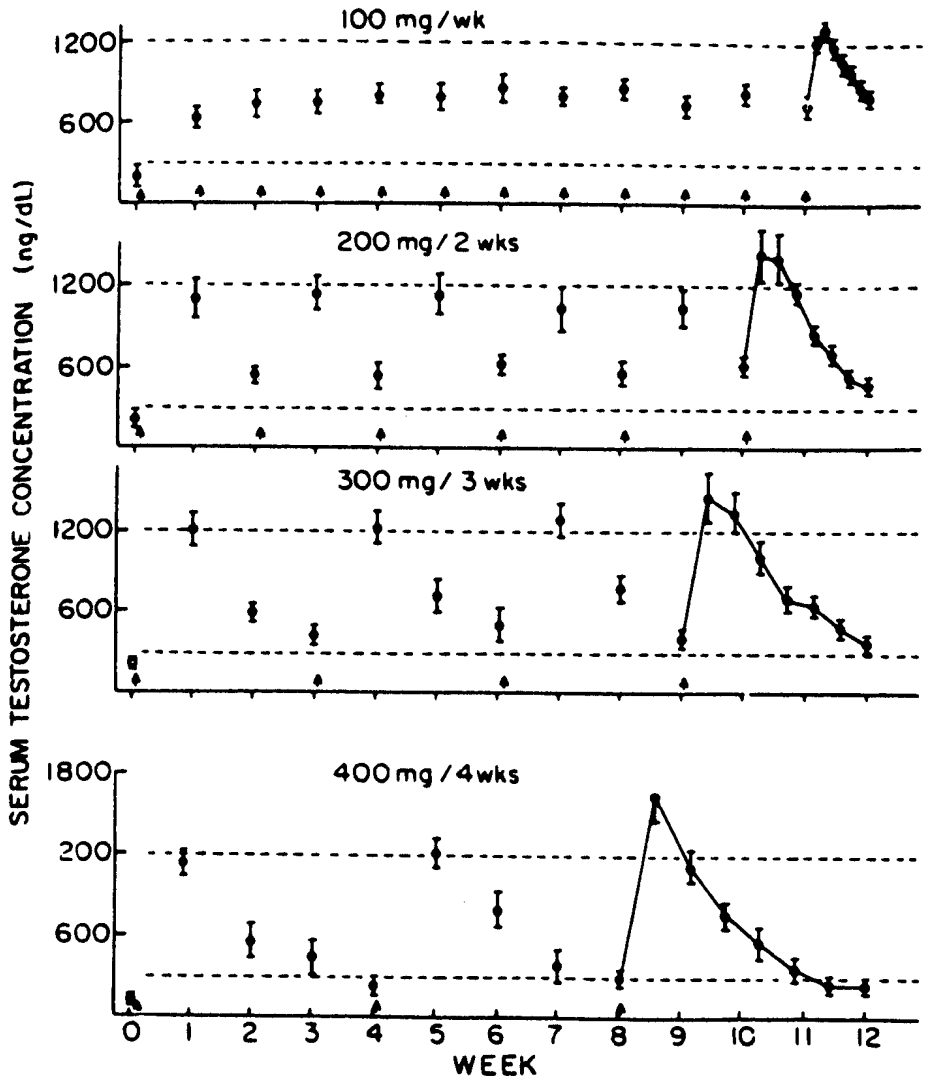


Fig. 2. Serum T concentrations during T replacement therapy in adult primary hypogonadal men. T enanthate was administered by intramuscular injection (arrows) for 12 wk in four dosage regimens: 100 mg weekly; 200 mg every 2 wk; 300 mg every 3 wk; and 4000 mg every 4 wk. Blood was sampled weekly until the last dose and more frequently thereafter. (From ref. *80.*)

Similar results were reported by Jockenhovel et al. *(87)* who implanted 6- to 200-mg fused crystalline T pellets in the subdermal fat tissue of the abdomen in hypogonadal men. An initial peak was observed on the first day of administration; thereafter, a stable plateau lasted for 63 d. On average T values fell below the normal range by 180 d but did not return to baseline for about 300 d. Serum estradiol and DHT were elevated from d 21 to d 105, and SHBG was decreased from d 21 to d 168. Thus, implants of T pellets have potential for both T replacement therapy, as well as reversible male contraception.

Transdermal Testosterone

Transdermal creams containing T have been used in the treatment of microphallus in children *(88)*. The applications probably are effective because of systemic absorption rather than local absorption in the penis. As yet, a widespread clinical trial with these preparations has not been reported *(89)*.

Table 5
Pharmacokinetics and Safety of Androgens

Preparation	*Peak*	*Trough*	*T monitoring*	*DHT*	*Estradiol*	*Liver dysfunction*	*HDL cholesterol*	*Skin irritation*
T propionate	1 d	2–3 d	None	Dose depend.	Dose depend.	None	Dose depend.	None
T enanthate	1–2 d	10–14 d	1 wk	Dose depend.	Dose depend.	None	Dose depend.	None
T cypionate	1–2 d	10–14 d	1 wk	Dose depend.	Dose depend.	None	Dose depend.	None
T buccilate	2–4 wk	12–14 wk	4–6 wk	Dose depend.	Dose depend.	None	Dose depend.	None
T pellets	1 mo	6 mo	3–4 mo	Dose depend.	Dose depend.	None	Dose depend.	None
T undeconoate	2–6 h	2–6 h		Increased	Normal	None	Dose depend.	None
T cyclodextrin	1 h	6 h	2–4 h	Normal	Normal	None	Modest	None
MethylT	1.5–2 h	4–5 h	None	Low	Low	Yes	30% dec.	None
Fluoxymesterone				Low	Low	Yes		None
Mesterolone				Low	Low	None		None
T gel	20–24 h	d	24 h	Normal	Normal	None	Modest	Minimal
T scrotal	3–5 h	20–24 h	12 h	Elevated	Normal	None	Modest	Minimal
T nonscrotal	6–8 h	24 h	12 h	Normal	Normal	None	Modest	Yes
DHT topical	4–8 h	20–24 h	DHT 12 h	Elevated	Low	None	Modest	Minimal

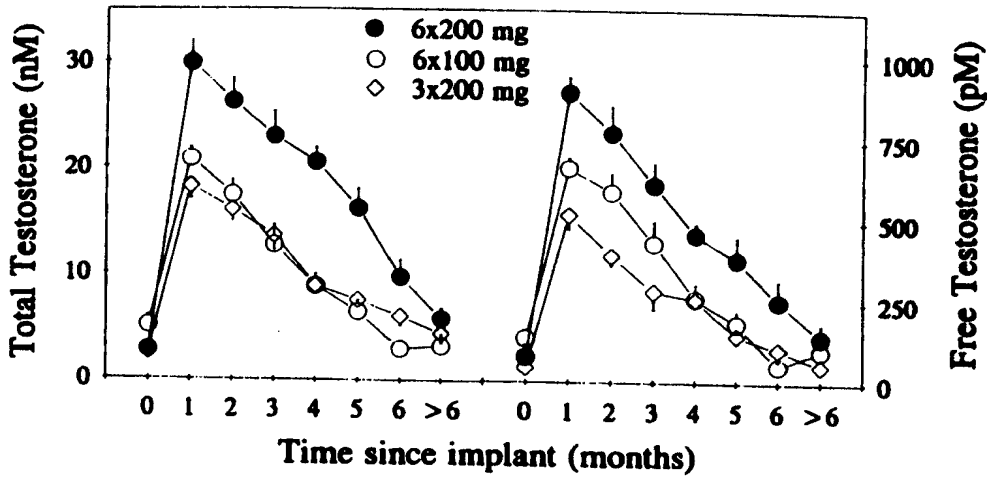


Fig. 3. Plasma total (left) and free (right) T following a single implantation in 43 hypogonadal men. (From ref. *86*).

Percutaneous DHT in Hypogonadal Men

A 125-mg dose of hydroalcoholic gel of DHT applied twice daily to the skin can produce sustained concentrations of DHT *(90–92)*. The ratio of DHT/T ratio increased to around 5 (normal ranges between 0.1 and 0.2), and serum T, estradiol, and SHBG concentrations did not increase; no change in gonadotropins was observed *(92)*. Treatment of hypogonadal men reportedly improved virilization and sexual function *(93)*, and a moderate decrease in plasma low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels was observed. DHT therapy did not result in enlargement of the prostate as determined by ultrasound study *(92,94)*.

Transdermal Testosterone

Trans-Scrotal Testosterone

Scrotal skin is at least five times more permeable to T than other skin sites. Testoderm® or Testoderm® With Adhesive will only produce adequate serum T concentrations if applied to scrotal skin. The 60-cm^2 and 40-cm^2 Testoderm patches applied to the scrotum of hypogonadal men delivers 4 and 6 mg, respectively, of T daily *(95)*. Peak T concentrations increased progressively during the first 3 wk and then remained stable. Although DHT concentrations remained elevated, the normal range androgen concentrations (T plus DHT) and estradiol were achieved in 80% of hypogonadal men *(28,95–101)*.

Nonscrotal Testosterone Patch Therapy (Androderm)

Pharmacokinetics. After two 2.5-mg or one 5-mg Androderm system(s) was applied daily to nonscrotal skin (back, abdomen, thighs, and upper arms) at about 10 PM, T was continuously absorbed during the 24-h dosing period. The serum T concentration profile mimicked the normal circadian variation observed in healthy young men (*see* Fig. 4) *(26,102,103)*. In addition, bioavailable T, DHT, and estradiol serum T concentrations (BT) measured during Androderm treatment paralleled the serum T profile (*see* Fig. 4) and remained within the normal reference range.

In clinical studies of Androderm, 93% of patients needed a dose of 5 mg daily to maintain normal concentrations of T; 6%, 7.5 mg daily; and 1%, 2.5 mg daily

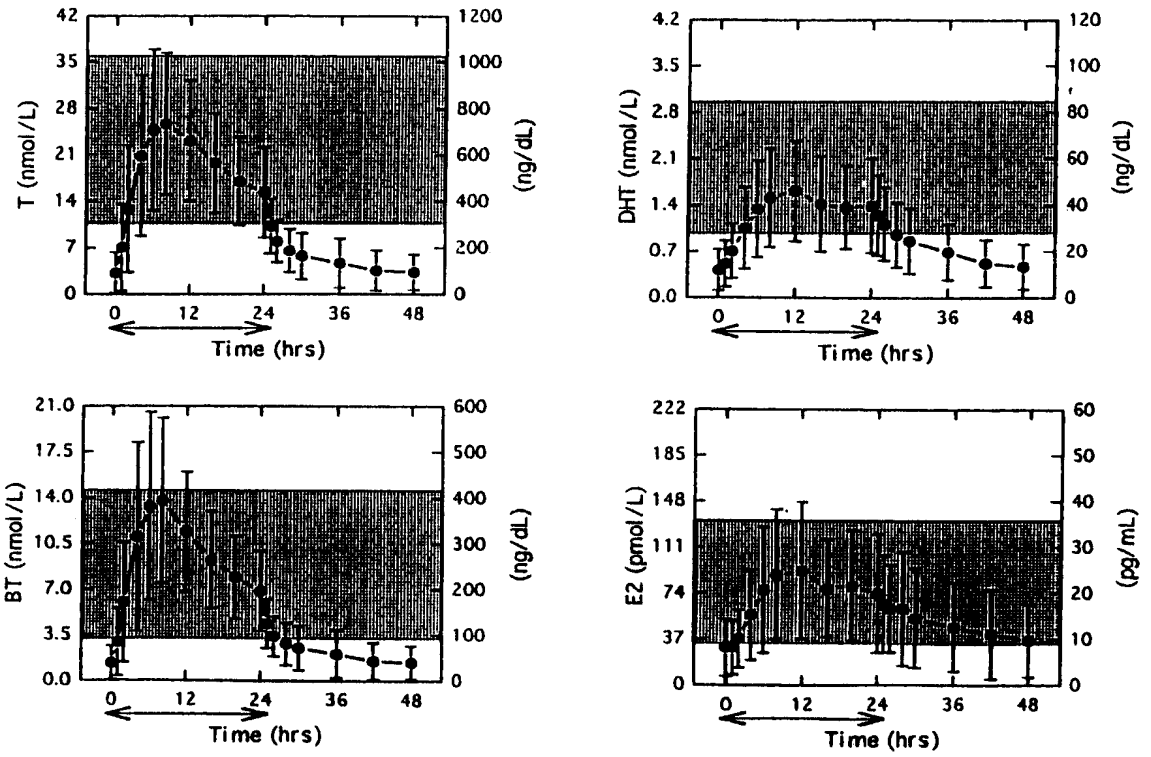


Fig. 4. Serum concentration profiles of T, BT, DHT, and E2 during and after the nighttime application of two TTD systems to the back of 34 hypogonadal men (mean ± SD). The shaded areas represent 95% confidence intervals for morning hormone levels in normal men between the ages of 20–65 yr. The arrow denotes the 24-h duration of TTD system application. (Reproduced with permission from ref. *26*.)

(26,102,103). Androderm therapy for 6–12 mo in men with primary hypogonadism had suppressed gonadotropins to normal range in about 50% of men *(26,102–104)*. Androderm therapy had positive effects on fatigue, mood, and sexual function as determined from questionnaires and nocturnal penile tumescence *(26,102–104)*.

Comparison with Intramuscular Testosterone. In a study of 66 patients previously treated with T injections, subjects were randomized to receive either Androderm or intramuscular T enanthate (200 mg every 2 wk) treatment for 6 mo *(102)*. The percent of normal range serum concentrations of T, bioavailable T, DHT, and estradiol was 82, 87, 76, and 81%, respectively, compared with 72, 39, 70, and 35%, respectively, for intramuscular T injections. Sexual function assessment and lipid profiles were comparable between groups.

Management of Skin Irritation. Chronic contact dermatitis resulting mainly from the alcohol component of the patch occurs in about 10% of men following several weeks of use of Androderm. Applying about two drops of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir has been shown to greatly reduce contact dermatitis and itching without significantly affecting T delivery *(105,106)*. The quantity of glucocorticoid applied and absorbed is insufficient to produce significant alteration of the hypothalamic–pituitary–adrenal axis. Hydrocortisone is less effective, and ointments should not be used because they will diminish T delivery.

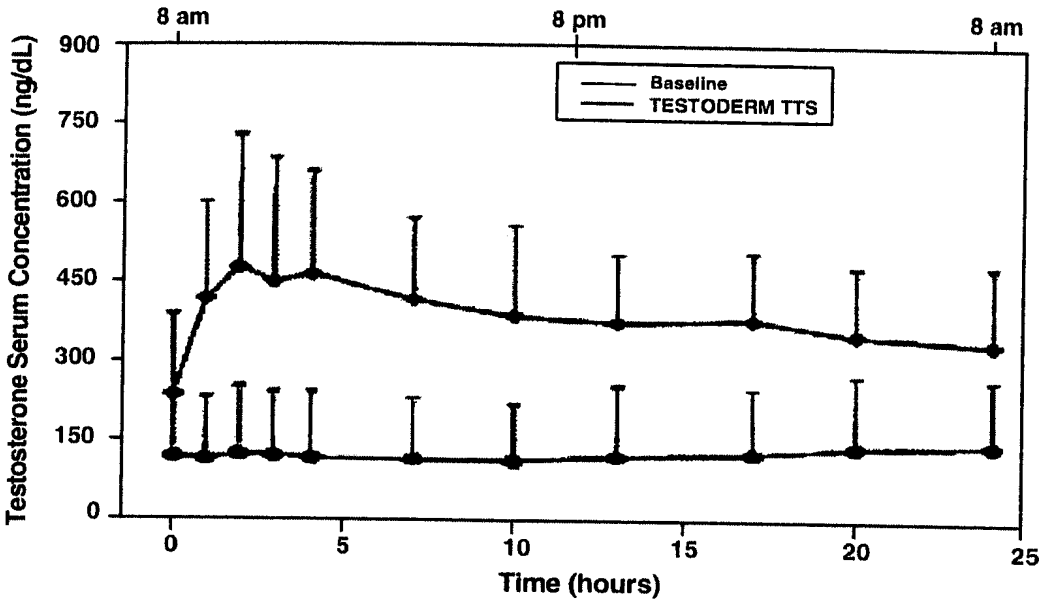


Fig. 5. Serum concentrations of T (mean±SD) during pretreatment baseline or while wearing a Testoderm TTS system on the upper buttocks (n = 32). Systems were applied at 0 h (8 AM) and removed 24 h later. (From Physician Desk Reference).

Testoderm TTS

Testoderm TTS applied each morning to the arm, back, or upper buttocks delivers physiologic amounts of T that exhibits a serum T circadian pattern resembling normal men (*see* Fig. 5). Following skin application, T concentrations peak at 2–4 h, continue to be absorbed during the 24-h dosing period, and return toward baseline within approx 2 h after removal of the system. In clinical trials, 94% of patients on Testoderm TTS treatment had peak (531 ng/dL) and average (366 ng/dL) serum T concentrations within the normal range. Applying two systems also doubles the amount of T delivered. When applied to the skin sites recommended (arm, back, or upper buttocks), the ratio of T to DHT or estradiol was also normal. The most commonly reported adverse events were application site reactions of transient itching (12%) and moderate or severe erythema (3%). All topical reactions decreased with duration of use.

AndroGel™

AndroGel™ 5 G, 7.5 G, or 10 G contain packets of 50 mg, 75 mg, or 100 mg of T, respectively. Approximately 10% of the applied T dose is absorbed across skin of average permeability during a 24-h period, resulting in circulating concentrations of T observed in normal men *(107)*. Figure 6 summarizes the 24-h pharmacokinetic profiles of T for patients maintained on 5 G or 10 G of AndroGel (to deliver 50 or 100 mg of T, respectively) for 30 d. The average (± SD) daily T concentration produced by AndroGel 10 G on d 30 was 792 (± 294) ng/dL and by AndroGel 5 G, it was 566 (± 262) ng/dL.

AndroGel dries quickly when applied to the skin surface, and the skin serves as a reservoir for the sustained release of T into the systemic circulation *(107)*. After the first 10 G dose, increases in serum T are observed within 30 min; and by 4 h of application, most patients have a serum T concentration within the normal range. Absorption of T into

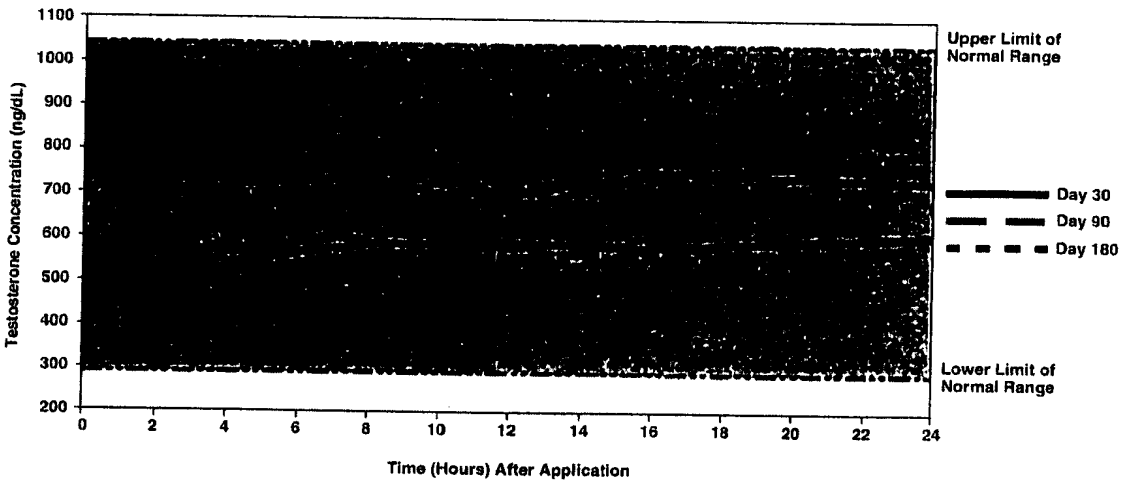


Fig. 6. shows the mean steady-state serum T concentrations in patients applying 5 g or 10 g Androgel once daily. (Data on file. Unimed Pharmaceuticals.)

the blood is sustained for the 24-h dosing interval, resulting in serum T concentrations approximating the steady-state level by the end of the first 24 h and achieving steady state by the second or third day of dosing.

Serum T levels decrease sharply after withdrawal of the patches, but serum T concentrations remain in the normal range for 24–48 h after the last application, and it take 5 d to return to baseline. Eighty-seven percent achieved an average serum T level within the normal range on treatment d 180.

Potential Partner Testosterone Transfer. Studies of the potential for dermal T transfer following AndroGel use between males dosed with AndroGel and their untreated female partners indicated that unprotected female partners had a serum T concentration more than twice the baseline value at some time during the study. When a barrier, such as a shirt, covered the application site(s), no transfer of T from the males to the female partners was observed.

Following AndroGel doses of 5 G/d and 10 G/d, DHT and estradiol concentrations increased in parallel with T concentrations, and the DHT/T ratio and estradiol levels stayed within the normal range. During AndroGel treatment, decreases of serum levels of SHBG were modest (1–11%), and serum levels of LH and FSH in men with hypergonadotropic hypogonadism fell in a dose- and time-dependent manner during treatment with AndroGel. Although skin reactions were reported in 3–5% of patients using AndroGel for up to 6 mo, none was severe enough to require treatment or discontinuation of drug.

Tostrex

A new T gel (Cellegy Pharmaceuticals, Inc.) has undergone clinical trials in about 200 hypogonadal men. The initial dose applied to the skin daily raises the serum concentrations of T on the first day of application, and reaches steady state by 14 d. A metered-dose canister allows adjusting the dose in 10-mg increments. Following adjustment of the dose based on the testosterone concentrations on d 14, over 90% of men achieved a 24-h concentration average within the normal physiologic range, as was the ratio of estradiol to T and DHT to T. Its safety profile in terms of chemistries, lipid profiles,

polycythemia, and prostate-specific antigen were comparable to other transdermal testosterone preparations on the market. Tostrex therapy for 6 mo resulted in improvement of hip and spine bone mineral density (BMD) of about 4%.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a polypeptide hormone produced by the human placenta and is composed of an α-subunit essentially identical to the α-subunits of the human pituitary gonadotropins (LH and FSH) and TSH. A specific α-subunit of hCG binds to the LH receptors on Leydig cells and stimulates endogenous T production from the testes. hCG also has some FSH activity that differs from pure LH.

In prepubertal boys between the ages of 4 and 9 yr with cryptorchidism not caused by anatomical obstruction, hCG treatment is done with the following regimen: 4000 USP units of hCG three times weekly for 3 wk; then 5000 U every 2 d for 4 injections followed by 15 injections of 500 to 1000 U for 6 wk; and then, 500 U three times a week for 4–6 wk.

Human chorionic gonadotropin is an alternative to T therapy in inducing pubertal development in boys and treating androgen deficiency in men with gonadotropin deficiency. In young prepubertal boys (e.g., 13–14 yr of age) presenting with hypogonadotropic hypogonadism and delayed puberty, hCG may be begun at a dosage of 1000–2000 IU intramuscularly. It is then slowly increased during the next 1–2 yr to the adult dosages of 1000–2000 IU intramuscularly, two to three times weekly (*see* Table 7). Some men with gonadotropin deficiency require either higher or lower dosages of hCG. Therapy in prepubertal boys can be monitored by assessing the clinical response to treatment by following the progression of virilization and growth and the serum T concentration, which should be maintained within the normal range for the desired Tanner stage of sexual development *(108)*.

Human chorionic gonadotropin therapy has two major advantages over T replacement therapy. Firstly, it stimulates growth of the testes, which may be important to boys with delayed puberty *(108)*. Secondly, it may stimulate sufficient intratesticular T production to facilitate initiation of spermatogenesis. hCG treatment has several disadvantages. It requires frequent injections, is expensive, elevates estradiol relative to T and may cause gynecomastia. If neutralizing antibodies to hCG are induced, they may reduce the efficacy of hCG or make it completely ineffective *(1,8)*.

POTENTIAL BENEFITS OF ANDROGEN THERAPY

Testosterone Replacement Therapy in Andropause (Aging Men)

(This topic will be covered in detail in Chapter 21.) Most studies have confirmed an age-related decline in T beginning in the fourth decade of life, and about 20% of men by age 60 have serum T concentrations of less than 300–350 ng/dL *(2–5,14,27,28,109–113)*. Because SHBG rises in aging men, bioavailable T (non-SHBG-bound) or free T concentrations may better reflect the deficiency of T than the total T concentration. Thus, free or bioavailable T measurements are recommended when the total T concentration is between 200 and 400 ng/dL.

Testosterone Effects on Body Composition

Studies in older men treated with T replacement have generally confirmed that body fat mass declines and lean body mass increases. Several forms of therapy have been used and

Table 7
Treatment of Male Hypogonadism

Group	*Goal of therapy*	*Plasma T*	*Preparation*	*Usual dose*
Delayed adolescence	Short-term maintenance, initial	100–300 ng/dL	hCG	500 IU im 1–2 times/wk
			Androderm	2.5 mg patch, 12 h at night
			TE or TC	50–100 mg q 3–4 wk
	Subsequent	300–400 ng/dL	Androderm	2.5 mg/daily
			TE or TC	100 q 2 wk
Adult	Long-term maintenance	400–1000 ng/dL		
Hypogonadotropic hypogonadism			GnRH[a]	5–30 μg sc q 2 h
Hypogonadism			hCG	1000–4000 IU im 1–3 times/wk
			Androderm, Testoderm, Androgel	5 mg/d
			Testoderm, Scrotal	4 or 6 mg/d
			TE or TC	200 mg q 2 wk or 100 q 1 wk im
	Subreplacement		Fluoxymesterone	5–10 mg/d po
			Methyltestosterone	5–25 mg daily
			T undecanoate[b]	200 po q 2 wk

[a]Experimental, requires programmed pump.
[b]Not available in the United States.
Abbreviations: hCG, human chorionic gonadotropin; GnRH, gonadotropin-releasing hormone; TE, T enanthate; TC, T cypionate.

include T esters, the scrotal patch, and a gel preparation. In addition, some aspects of muscle strength, fat-free mass, and visceral fat improved. These studies were relatively short and ranged in length between 3 and 18 mo. The studies are too small and of inadequate length to make it possible to compare one treatment modality to another *(114–117)*.

Muscle Performance and Wasting

In addition, the measurement of the triceps and quadriceps increased significantly as did muscle strength measured by one repetition maximum of weight lifting. These results are in agreement with cross-sectional studies in men with the AIDS wasting syndrome *(118)*. Testosterone therapy is used for management of weight loss and wasting associated with AIDS *(119–121)*. Administration of replacement doses of T to healthy hypogonadal and HIV-infected men improves lean body mass, muscle size, and maximal voluntary strength *(122)*. Sih et al. *(123)* reported improvement of bilateral grip strength in older hypogonadal men treated with T at 3, 6, 9, and 12 mo of therapy.

Mood

In elderly and younger hypogonadal men, T therapy improves spatial cognition, sense of well being, libido, fatigue, self-reported sense of energy ($49 \pm 19\%$ to $66 \pm 24\%$; $p = 0.01$) and sexual function ($24 \pm 20\%$ to $66 \pm 24\%$; $p < 0.001$) within the first 3 mo of initiation of therapy *(68,114,115,124–127)*.

Testosterone therapy *(68)* significantly decreases anger, irritability, sadness, tiredness, and nervousness while improving energy level, friendliness, and sense of well-being. Sih et al. *(123)* did find an improvement of memory with of T replacement.

Impotence

Impotence in hypogonadal men may be corrected in about 75% of men if the cause of impotence is androgen deficiency *(128)*. Some men have androgen deficiency and impotence caused by other factors. If several months of T therapy does not correct their impotence, other causes should be sought.

Leptin

Although serum T is negatively associated with leptin in men, the association is confounded with visceral and subcutaneous adipose tissue, fasting insulin, and sex hormones. Thus, T does not appear to be the major determinate of serum leptin in men *(129)*. In aging men, a rise of serum leptin levels occurs, and a strong association between serum leptin and adiposity is maintained *(130)*. Furthermore, T ester therapy significantly reduced leptin concentrations in elderly men *(123)*, normalizes elevated *ob* gene product leptin (OB) levels in hypogonadal men *(131)* and also decreases leptin concentrations in boys with delayed puberty *(132)*. The studies suggest the hypothalamic–pituitary–gonadal–adipose tissue axis is involved in body weight maintenance and reproductive function *(131,133)*.

Osteoporosis

Androgen Deficiency and Osteoporosis

Effects of Androgens in Normal Men. Androgens affect both by the peak bone mass achieved during development and the subsequent amount of bone lost. The dramatic increase in both cortical and trabecular bone density during puberty in boys *(134,135)* is attributed to the pubertal rise in T or one of its metabolites. During puberty, an increase in serum alkaline phosphatase heralds a rise in osteoblast activity and subsequent bone density increases. In normal boys, peak trabecular bone density is usually achieved by the age of 18 yr *(135)*, and peak cortical bone density is often reached a few years later. Bone density remains relatively stable in young adult males and then declines slowly after age 35 yr *(136)*; the bone loss is regulated by genetic, endocrine, mechanical, and nutritional factors.

Bone Density in Hypogonadal Men

Studies in Men with Primary Hypogonadism. Surgical or medical castration in men results in a reduction in BMD and elevated biochemical markers of bone turnover *(137,138)*. These findings suggest that gonadal steroid deficiency is associated with increased bone turnover and loss, leading to osteoporosis (*see* Fig. 7); other secondary causes are glucocorticosteroid therapy, skeletal metastases, multiple myeloma, gastric surgery, and anticonvulsant and neuroleptic treatment *(139–142)*.

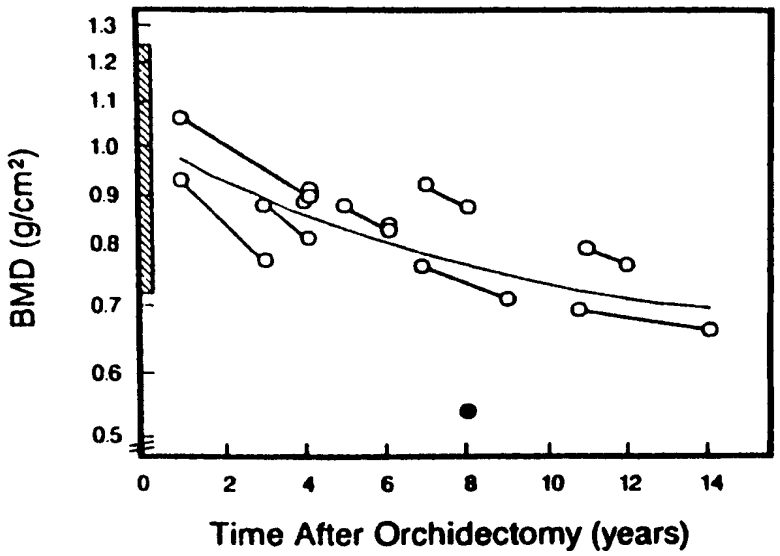


Fig. 7. Scattergram of lumbar spinal BMD as a function of time after orchidectomy in 12 men. In eight patients, the measurement was repeated after 1–3 yr. The hatched bar indicates the normal range for 20 men matched for age. The solid circle represents the value for one man who developed a hip fracture. (Reproduced with permission from ref. *137.*)

Although hypogonadism is found in up to 20% of men with vertebral crush fractures or osteoporosis, the clinical features of T deficiency may be subtle.

Aging and Osteoporosis

Osteoporosis is one of the leading causes of morbidity and mortality in the elderly. Bone is lost with advancing age in both men and women, leading to an increased incidence of osteoporotic fractures of the forearm, vertebral body, and femoral neck. Although aging women lose more bone than men, aging men still lose 30% of their trabecular bone and 20% of their cortical bone *(136)*. Thus, despite lower rates of osteoporosis in men than in women, one-fifth of all hip fractures occur in men and hypogonadism is one of the most common underlying causes *(143,144)*. Further study is needed to clarify this association between bone loss and T deficiency, but androgen replacement in aging hypogondal men does improve BMD *(115,123)*.

Men with acquired hypogonadism, idiopathic hypogonadotropic hypogonadism (IHH) and constitutionally delayed puberty have reduced BMD and may be at increased risk for osteoporosis. In boys with delayed puberty or IHH, T may not result in normal bone accretion in adulthood *(145–147)*. Finkelstein et al. *(147)* postulated that inadequate bone accretion rather than accelerated bone loss may account for the diminished adult bone mass of patients with delayed puberty or IHH. Both radial and spinal bone mineral density were significantly lower in men with histories of delayed puberty than in normal controls (see Fig. 8A,B). These results establish that T replacement in young or elderly hypogonadal men improve BMD.

Glucocorticoids, Androgens, and Osteoporosis

Osteoporosis is associated with both hypogonadism and corticosteroid therapy. In addition, glucocorticoid therapy may cause a variety of adverse systemic effects, including adrenal suppression, dermal thinning, and a reduction in total bone calcium. Test-

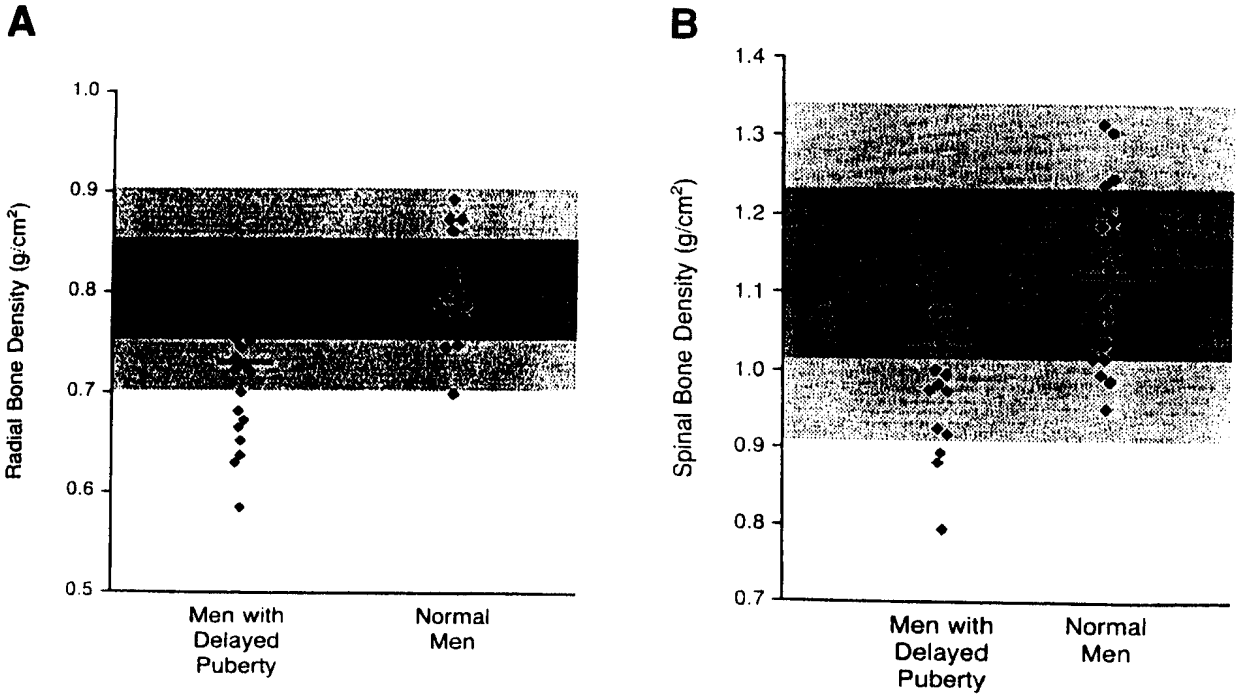


Fig. 8. Radial bone density **(A)** and spinal bone density **(B)** in 23 men with histories of delayed puberty and 21 normal controls. The horizontal lines indicate the group means, and the shaded areas indicate the mean ± 1 SD and ± 2 SD. for the normal men. (Reproduced with permission from ref. *147.*)

osterone levels are reduced about 33% by long-term oral prednisolone treatment, but are minimally affected by therapeutic doses of inhaled corticosteroids *(148–152).*

Hypogonadism, Osteoporosis, and Testosterone Therapy

Recently, Behre et al. *(153)* reported on the long-term effects of androgen-replacement therapy on BMD in hypogonadal men. During the first year of therapy, BMD increased 26% (see Figs. 9 and 10). In 72 hypogonadal men, long-term therapy maintained BMD in the age-dependent reference range independent of whether the patients had primary or secondary hypogonadism. Adequate T-replacement therapy with injection of T esters, oral or transdermal preparations will improve BMD, markers of bone formation and resorption and also treat osteoporosis in hypogonadal men *(115,116,154,155).*

Mechanism of Action of Androgens on Bone

The mechanism(s) whereby androgens affect bone density is still unclear. Testosterone can be converted to DHT by human bone in vitro. However, inhibition of DHT formation by administration of an inhibitor of 5α-reductase has no effect on bone mass in humans *(156)* or rats. The aromatization of T into estrogens may be important for many of the effects of T on bone: (1) Estrogen receptors are present in human osteoblasts *(157–164)*; (2) estrogens appear to maintain bone mass in castrated male-to-female transsexuals; (3) men with complete estrogen resistance as a result of a genetic defect in the estrogen receptor or aromatase deficiency have severe osteopenia despite normal T levels and complete virilization *(165)*. These findings provide compelling evidence that

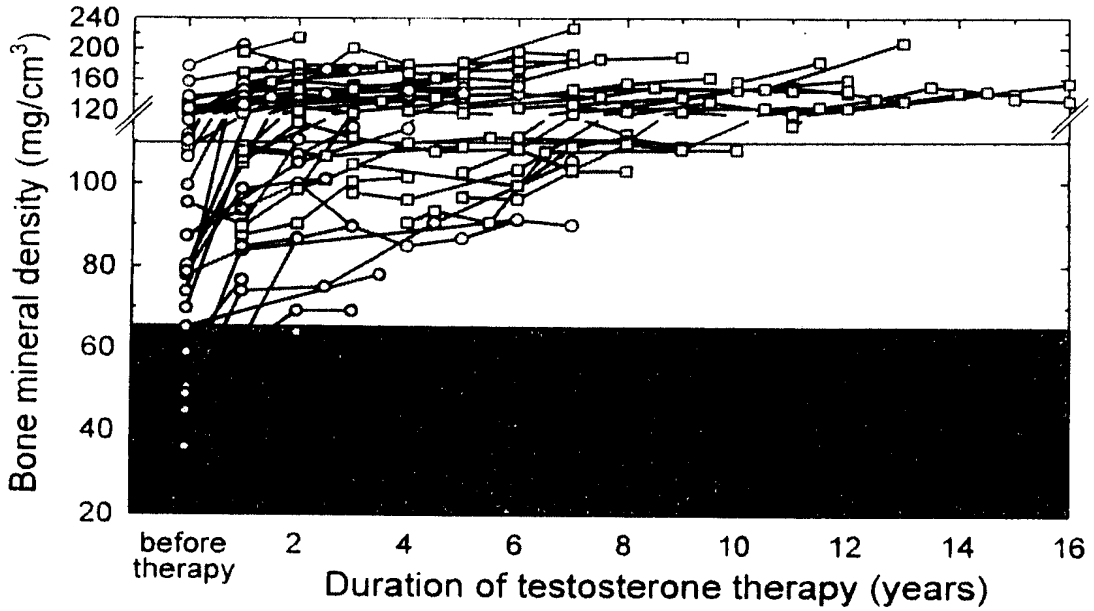


Fig. 9. Increase in BMD during long-term T-substitution therapy up to 16 yr in 72 hypogonadal patients. Circles indicate hypogonadal patients with first QCT measurement before initiation of T-substitution therapy, squares show those patients already receiving T therapy at the first QCT. The dark shaded areas indicates the range of high fracture risk, the unshaded area shows the range without significant fracture risk, and the light shaded area indicates the intermediate range where fractures may occur. (Reproduced with permission from ref. *153*.)

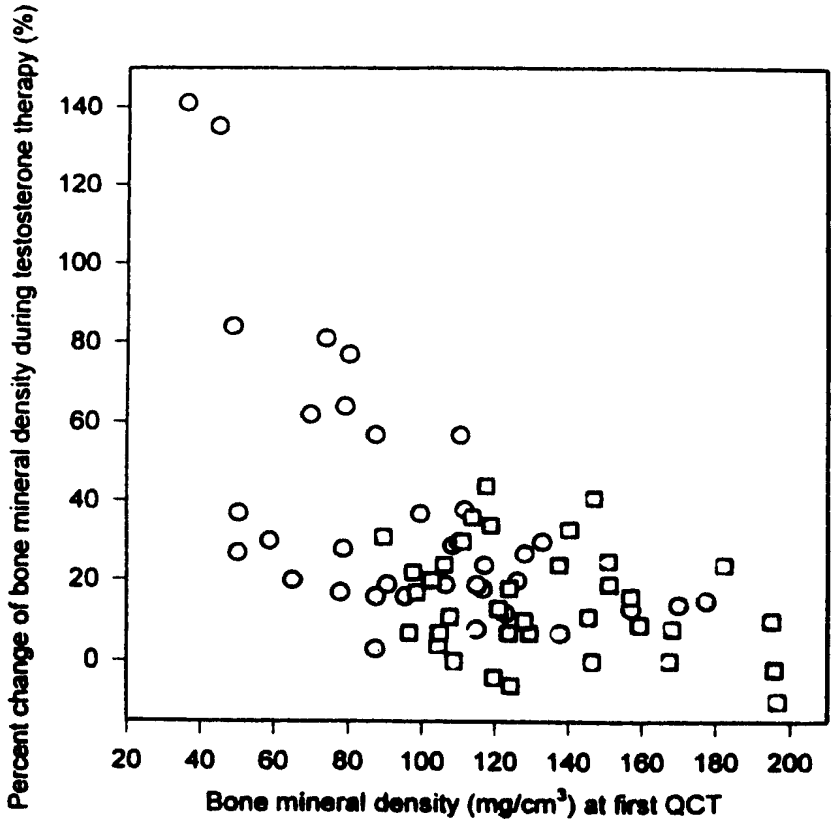


Fig. 10. Correlation between BMD at the first QCT measurement and percent change in BMD during T-substitution therapy. Circles indicate hypogonadal patients with first QCT measurement before initiation of T-substitution therapy; squares show those patients already receiving T therapy at the first QCT. (Reproduced with permission from ref. *153*.)

estrogens are required for a normal peak bone mass in men. However, cortical bone mineral density is higher in men than in women *(135)*; whether this is secondary to the larger muscle mass in men (than in women) is unknown.

Therapy of Androgen-Deficiency Bone Loss

Androgen-replacement therapy has been shown to increase in BMD in hypogonadal men and particularly those with skeletal immaturity *(147,166)*. The studies of Snyder et al. *(115)* suggest that improvement in BMD is achieved with a eugonadal serum concentration of T (>350 ng/dL) *(115)*, so even in men with modest decreases of serum T concentrations, osteoporosis is observed. Long-term studies are needed to determine if T therapy will prevent osteoporosis without causing undue risks. Although it appears that normalization of serum T concentrations is satisfactory therapy for osteoporosis of hypogonadism, studies comparing various forms of androgen-replacement therapy on management and prevention of osteoporosis should be conducted. For some men, androgens are contraindicated and designer estrogens or bisphosphonates may provide benefits in preventing bone loss after induction of hypogonadism with medical or surgical therapy.

PRECAUTIONS OF ANDROGEN THERAPY IN AGING MEN

Several complications of androgen replacement therapy have been reported. With T preparations, the risk of adverse influences on water retention, polycythemia, hepatotoxicity, sleep apnea, prostate enlargement, and cardiovascular appear small.

Water Retention

Some weight gain is common with androgen-replacement therapy, but the occurrence of peripheral edema, hypertension, and congestive heart failure is uncommon *(167)*.

Polycythemia

Androgens stimulate erythropoiesis, which accounts for higher hematocrits in normal men compared to hypogonadal men. Because older men tend to have lower hematocrits than younger men, the risk of polycythemia is low *(167)*. Although Sih et al. *(123)* reported that 24% of older men treated with injections of T cypionate (200 mg every 2 wk) had hematocrits above 52%, T-patch therapy appears to have a lower risk for hematocrit elevation than injections of 200 mg of T esters given every 2 wk *(168)*. Men with a history of polycythemia should be monitored closely, and those without a history of polycythemia should have periodic screening of the hematocrit.

Sleep Apnea

Testosterone-replacement therapy has been associated with worsening of sleep apnea, apparently without affecting upper airway dimension *(169,170)*.

Recent studies of T therapy in older men have not reported sleep apnea as a complication. However, men with a history of sleep apnea were generally excluded from participation *(166)*.

Serum Lipids

An elevation of total cholesterol and a suppression of HDL are known risk factors for cardiovascular disease. Many studies have shown a reduction in total cholesterol and

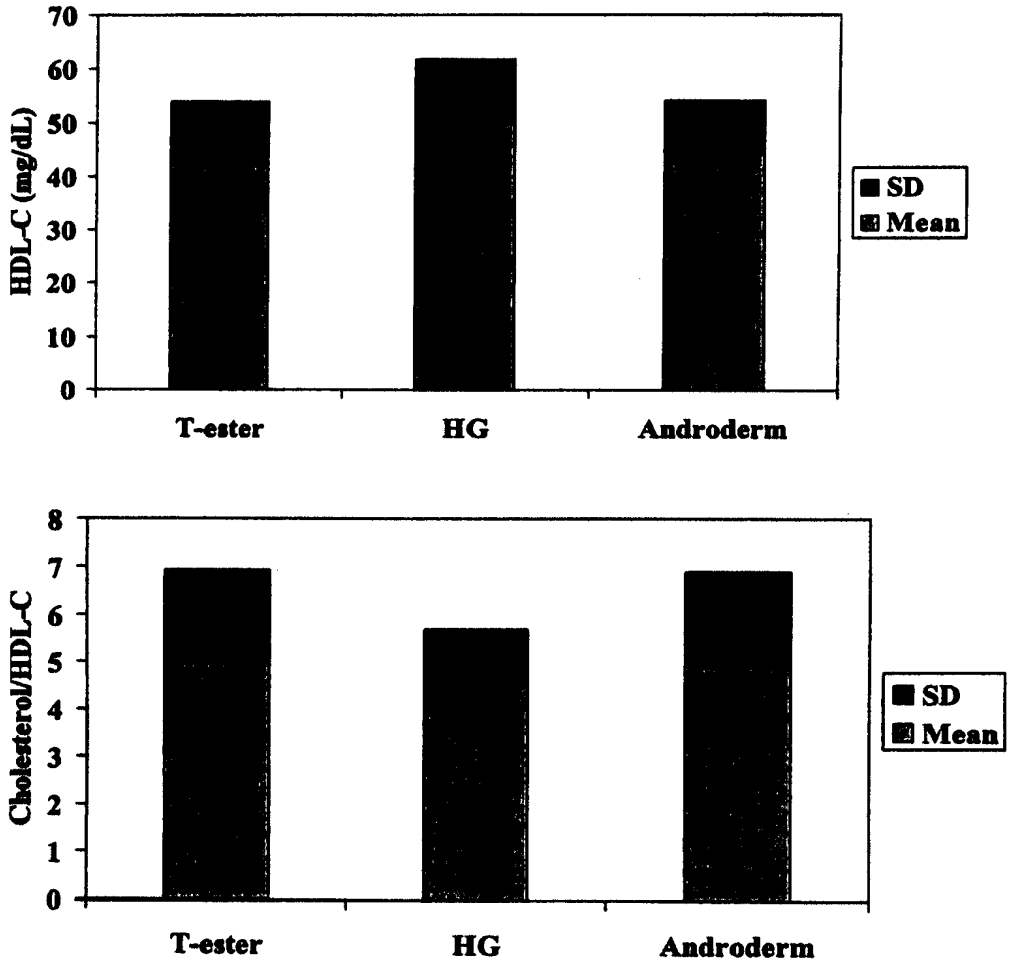


Fig. 11. Lipid changes during Androderm and T enanthate therapy in hypogonadal men. Mean ± SE. (Reproduced with permission from ref. *26*.)

LDL cholesterol in response to androgen replacement therapy without an adverse profile for HDL cholesterol. Higher than usual replacement doses of T have been associated with adverse lipid profiles *(171–174)*.

Androgen Effects on Plasma Lipids

Compared to an androgen-withdrawal interval of 8 wk, Androderm treatment for 1 yr decreased cholesterol 1.2% and HDL 8%, but increased the ratio of cholesterol to HDL 9% *(102)* (*see* Fig. 11). Other studies with transdermal (patches and gel systems) androgen-replacement therapy have shown comparable results *(114,115,175)*. However, these results were not significantly different from those measured during the intramuscular injection baseline treatment phase. In the study of Dobs et al. *(175)*, during the T replacement phases, serum HDL levels showed a strong negative correlation with BMI and other obesity parameters. Thus, the results of transdermal T replacement on serum lipids were consistent with physiologic effects of T observed in eugonadal men.

In other studies in healthy younger men, Golderberg et al. *(176)* reported that treatment with a GnRH agonist produced elevation of HDL cholesterol, apo AI, and apo B levels, and no change in triglycerides. If androgen replacement is done along with GnRH

therapy, the rise in HDL cholesterol can be aborted *(171–174,177)*. GnRH plus 100 mg/wk of TE produced only a slight decrease in HDL cholesterol without a significant change in HDL2 or 3 and apo AI. Estradiol was shown to be important in preventing the drop in HDL2 in men treated with T *(173)*. The relationship between androgen therapy and changes in plasma lipids is complex because androgens also are associated with changes in body composition and metabolic variables *(178)*. In older men treated with T cypionate or enanthate, no adverse effects of therapy were reported for cholesterol, LDL, HDL, or triglycerides *(179,180)*.

Oral methylT replacement therapy decreases HDL by more than 30%, with striking changes in the HDL2 subfraction and apo AI and AII. LDL cholesterol rises about 30–40% with a decrease of 65–80% in Lp(a) levels (at least in women) *(181,182)*. The more profound influence of anabolic androgens compared with parenteral T preparations appears to be related to the metabolism of T to estradiol and to lack of first-pass liver effects. Thus, oral nonaromatizable androgens have a greater suppression of HDL cholesterol than do aromatizable androgens such as T.

Prostate Disease

Benign Prostate Enlargement

Progressive growth of the prostate occurs in both the transition and peripheral zones of the prostate as men age *(183–186)*. In both normal and hypogonadal aging men, androgen withdrawal results in a significant reduction in prostate volume of both zones (*see* Fig. 12) *(185)*. Meikle et al. *(185)* found a high correlation with the volume of the prostate and age in men receiving T enanthate during androgen withdrawal and during androgen therapy with Androderm. Following 8 wk of androgen withdrawal, Androderm treatment resulted in growth of the prostate to the size observed during T enanthate therapy. Over the next 9 mo, further enlargement was not observed. In a cross-sectional study, Behre et al. *(187)* reported that in untreated hypogonadal men, no significant correlation existed between prostate volume and age. In contrast, T-treated men and normal men showed a positive correlation with prostate volume and age, and no significant age-adjusted differences were observed between the T-treated men and normal controls (*see* Fig. 13) consistent with the studies of Meikle et al. *(185)*. Serum concentrations of PSA were not elevated above those expected in men of comparable age, which is consistent with results reported recently by Sih et al. *(123)*. Jin and associates *(188)* observed that despite adequate long-term androgen-replacement therapy in men with androgen deficiency, they had reduced volumes of the central and peripheral zones as well as the total volume compared to age-matched controls, suggesting that age combined with T is important for prostate growth in mid-life. Because lower urinary tract symptoms are strongly influenced by hereditary factors and prostate volume *(189)*, it is not surprising that androgen-replacement therapy is associated with symptomatic prostate symptoms. Although there are limitations in study design, these observations do not suggest that androgen-replacement therapy will cause growth of the prostate beyond what will occur in men with normal gonadal function.

Prostate Cancer

Prostate cancer is an androgen-responsive cancer, but evidence that T therapy causes prostate cancer is lacking *(190,191)*. An undiagnosed prostate cancer may grow in response to T therapy. A PSA and digital rectal examination is recommended in men age

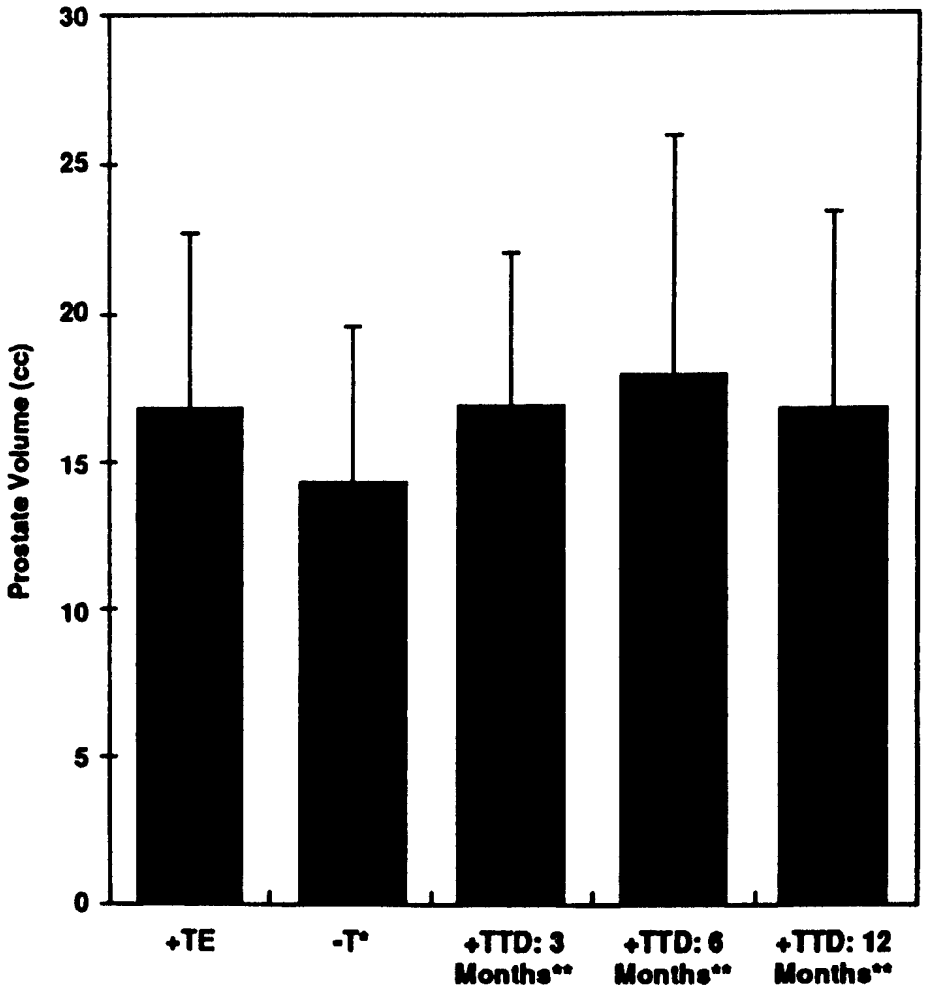


Fig. 12. Prostate volumes measured by TRUS. (T = T; TE = T enanthate; TTD = T transdermal system.) (Reproduced with permission from ref. *185*.)

40 and over before initiation of androgen-replacement therapy for hypogonadism. Further, screening for prostate cancer in men on T therapy should follow the usual guidelines for normal men of comparable age. None of the studies of androgen-replacement of men has shown an increased risk of prostate cancer. However, long-term controlled studies are needed in aging men.

OTHER CONSIDERATIONS OF TREATMENT OF ANDROGEN DEFICIENCY

The main use of androgen-replacement therapy is in the management of men with T deficiency. The cause of the hypogonadism should be established to determine if it might be reversible. If so, therapy should be directed at correction of the underlying cause. For example, hyperprolactinemia from a pituitary tumor can be treated with bromocryptine, which will often correct the T deficiency. Some tumors of the pituitary or hypothalamus may require surgical or irradiation therapy. Thus, in addition to secondary or tertiary hypogonadism, other deficiencies, such as ACTH, growth hormone, and thyroid-stimu-

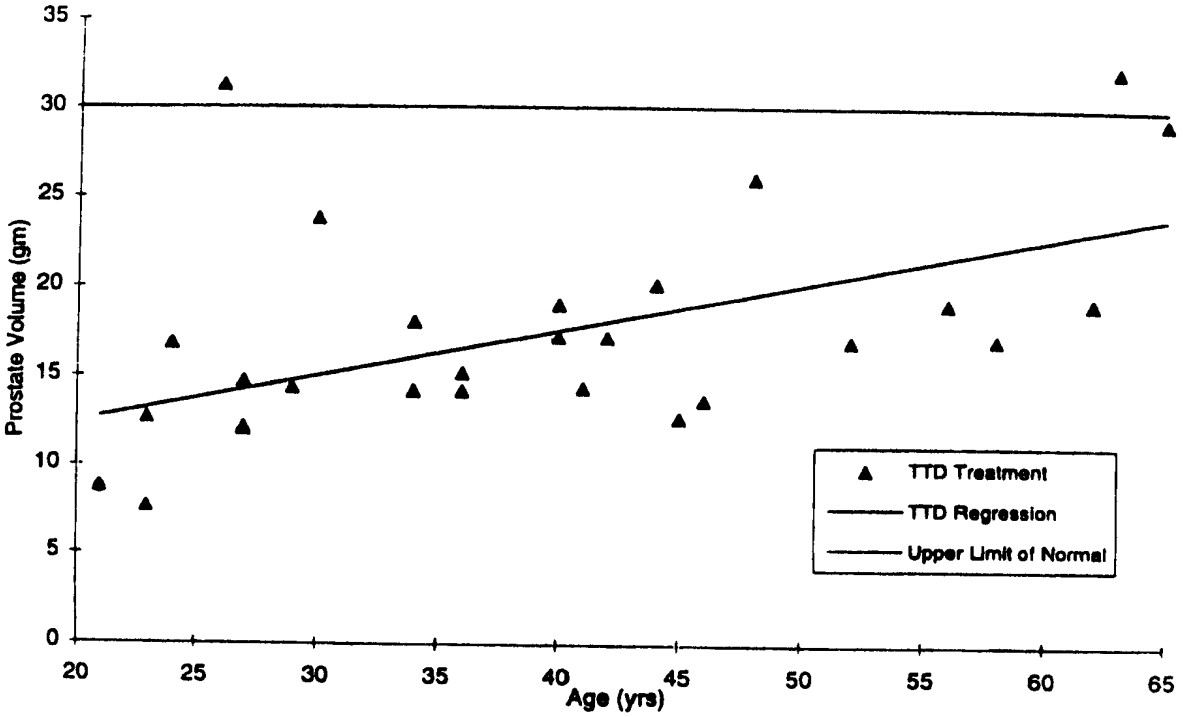


Fig. 13. Linear regression of prostate volume with age. Prostate volume correlated significantly with age during 1 yr of T transdermal system treatment ($r = 0.55$, $p < 0.01$). (IM = IM; TTD = T transdermal system.) (Reproduced with permission from ref. *185*.)

lating hormone (TSH) may exist and require management. Systemic illness and glucocorticoid therapy will cause hypogonadism, and depending on the clinical situation, androgen-replacement therapy may be considered in such patients. In aging men, androgen replacement therapy requires the usual monitoring for diseases incident to age but may offer benefits in bone preservation, lean body mass, mood, and intellectual and sexual function. For men who desire fertility at some time in their life, hormonal therapy directed at enhancing spermatogenesis may be successful. After fertility therapy is deemed a success or a failure, resumption of conventional T therapy is then indicated.

Severe gynecomastia or small testes may contribute to psychological problems or social embarrassment for some hypogonadal boys and men. Gynecomastia usually does not regress and may worsen during hormonal replacement therapy of hypogonadism; plastic surgery (reductive mammoplasty) is a reasonable alternative. Some patients with secondary hypogonadism may have enlargement of the testes in response to gonadotropin therapy, but such therapy is not indicated in men with primary hypogonadism, such as those with Klinefelter's syndrome who have extremely small testes. Surgical implantation of testicular prostheses is an option for some men and may have psychological benefits.

SUMMARY OF ANDROGEN-REPLACEMENT THERAPY

The hormone replacement goals for management of male hypogonadism depend on both the cause and the stage of sexual development in which gonadal failure occurs (Table 7). Androgen-replacement therapy is indicated to stimulate and sustain normal secondary sexual characteristics, sexual function, and behavior in prepubertal boys and

men with either primary or secondary hypogonadism. Several options for replacement therapy are available in various countries, and the availability of those preparations should be taken into consideration by the clinician before therapy is instituted. The goal is to normalize physiology as closely as possible and at the lowest cost. All of these factors influence the decision, which is shared with the physician and patient.

The available T esters for intramuscular injection (T propionate, T enanthate, T cypionate, and T cyclohexane carboxylate) do not achieve physiologic serum T profiles for the treatment of male hypogonadism (*see* Table 7). However, they do achieve therapeutic responses when administered in appropriate doses and intervals. Doses and injection intervals frequently prescribed in the clinic result in initial supraphysiologic androgen levels and subnormal levels prior to the next injection. Injections of 100 mg of T enanthate or cypionate intramuscular at weekly intervals would more closely approximate normal physiology than 200–250 mg every 2–3 wk. However, an injection frequency more often than 2 wk may be unacceptable to many patients. Further, because both the short-acting and intermediate-acting esters show maximal serum concentrations shortly after injection, there is no advantage in combining short-acting T esters (i.e., T propionate) and longer-acting esters (i.e., T enanthate) for T-replacement therapy.

Of the clinically available injectable androgen esters, 19-norT hexoxyphenylpropionate shows the best pharmacokinetic profile. However, as a derivative of the naturally occurring T, 19-norT might not possess its full pharmacodynamic spectrum and, therefore, is not an ideal drug for treatment of male hypogonadism *(78,79)*.

Oral administration of T undecanoate is easy to administer, and a new formulation may reduce the need for multiple daily doses. The most favorable pharmacokinetic profiles of T are observed using either the transdermal patch or gel systems. The scrotal system has the disadvantage of supraphysiologic DHT concentrations and is not easy to use for many patients. Daily administration of Androderm, in the evening results in serum T concentrations in the normal range, mimicking the regular circadian rhythm. The nontranscrotal system has the disadvantage of local skin reactions, which can often be successfully managed with topical glucocorticoid administration. Testoderm, TTS also produces a circadian variation of T delivery and satisfactory replacement therapy. Patch adherence is a problem for many patients, which reduces its therapeutic efficacy. Skin reactions are much less with Testoderm, TTS than with Androderm. Androgel, also produces T levels within the normal range but does not have a distinct diurnal delivery pattern. A newer gel preparation should be available soon. Skin reactions are much less frequent with gels than with patch systems, and because the gels are transparent after application, they are more discreet. Person-to-person transfer is a potential problem with gels, but this problem can be avoided with appropriate precautions. Currently, several satisfactory options for T-replacement therapy are available to clinicians in various countries. Of course, the treatment must be tailored for each patient, and important considerations include ease of use, physiologic replacement, few side effects, and cost. All of these should be discussed with the patient before making the selection. Although T esters, T enanthate, and T cypionate are effective, safe, and the least expensive androgen preparations available (particularly if self-administered), they require administration by injection into a large muscle. Testosterone enanthate and cypionate are considered equally effective and have been popular in the past for treatment of hypogonadal men (*see* Table 7).

Prepubertal

Androgen-replacement therapy in prepubertal hypogonadism is usually started at about 14 yr of age. The earliest sign of puberty in boys is enlargement of the testes. Increases in serum LH and T levels (initially at night) are the hormonal signals that also indicate the onset of puberty *(1,8)*. Growth, virilization, and psychological adjustment are evaluated clinically during androgen-replacement therapy. Severe emotional and psychological distress in affected boys and their families makes earlier institution of androgen replacement therapy a prudent choice. It is often difficult to accurately distinguish between simple delayed puberty and hypogonadism. Therefore, only transient androgen therapy is used until permanent hypogonadism is established, which then dictates continuous treatment to induce puberty and maintain sexual function *(1,8)*. In young boys with delayed puberty and also markedly retarded bone age and short stature, excessive androgen treatment causes rapid virilization and increases in long bone growth and also may lead to premature closure of epiphyses, resulting in compromised adult height *(1,8)*.

In boys with simple delayed puberty, gradual replacement therapy with T is usually begun using a 50 or 100 of T enanthate or cypionate intramuscularly monthly *(1,8)* or 2.5 mg daily of transdermal T. The design of the regimen in boys is to duplicate the changes in T that occur with puberty in normal boys and thus gradual virilization and progression of secondary sexual development. This regimen will stimulate long bone growth and initiate virilization without interfering with the onset of spontaneous puberty. If simple delayed puberty or hypogonadism is diagnosed, the dosage of T ester is increased to 50–100 mg every 2 wk or 2.5 mg of Androderm, nightly for 12 h for approx 6 mo. It is then stopped for 3–6 mo for assessment of the spontaneous onset and progression of puberty. If spontaneous pubertal development and growth do not occur, androgen therapy is reinstituted for another 6 mo with 100 mg of T ester every 2 wk or 2.5 mg of Androderm, daily. This will produce further virilization; full virilization can be achieved over the next few years with full adult replacement doses. Full adult replacement dosages are seldom needed in those with simple delayed puberty.

Adults

In adults with hypogonadism, androgen-replacement therapy is begun by administering a 5 mg delivery dose of a patch or gel system or 200 mg of either T enanthate or cypionate, intramuscularly every 2 wk. Figures 1 and 2 display the fluctuations of serum T concentrations after intramuscular injection of 200 mg of either ester. Injectable T preparations result in T levels at or above the normal range 1–4 d after administration and then gradually fall over the subsequent 2 wk and may be below the normal range before the next injection. Administering 100 mg of T enanthate or cypionate intramuscularly weekly produces a better pattern of T levels, but higher doses at less frequent intervals deviate much more from physiologic normal T range *(74,80)*. Patients, family members, or friends can be taught to give deep intramuscular injections of T esters; otherwise, injections by nursing personnel in the clinic are needed.

The therapeutic efficacy of androgen replacement is assessed by monitoring the patient's clinical and serum T responses *(1,8)*. Variability in response to T therapy in hypogonadal men in libido, potency, sexual activity, feeling of well-being, motivation, energy level, aggressiveness, stamina, and hematocrit is considerable and may occur during the first few weeks to months of androgen-replacement therapy. Body hair,

muscle mass and strength, and bone mass increase over months to years. In a sexually immature, eunuchoidal man, androgen replacement also stimulates development of secondary sexual characteristics and long bone growth. Many months to years may be required to achieve the mature adult status.

If injectable forms of T are used, T levels during therapy should be in the mid-normal range 1 wk after an injection and above the lower limit of the normal range preceding the next injection. In some hypogonadal men treated with T esters, disturbing fluctuations in sexual function, energy level, and mood are associated with fluctuations in serum T concentrations between injections. Thus, some patients may complain of reduced energy level and sexual function a few days before their next T injection and have serum T levels below the eugonadal range at that time. Shortening the dosing interval of T ester administration from every 2 wk to every 10 d is recommended in these patients.

With patch and gel systems, a beginning dose of 5 mg of T is recommended for adults; however, a smaller dose may be appropriate for some elderly men. Therapeutic efficacy of patch and gel systems can be monitored by measurement of serum T concentrations about 12 h after application and continued daily for 7–14 d. If levels are not in the eugonadal range, then the dose should be adjusted. Men who have been hypogonadal for prolonged intervals may experience alarming changes in sexual desire and function, which may cause stress in a sexual relationship *(1,8)*. Counseling of patients and their partners before beginning androgen replacement is recommended to help reduce or alleviate these adjustment problems. Beginning with a lower replacement dose may be wise, particularly in an elderly hypogonadal man.

As discussed in detail elsewhere, men with prepubertal hypogonadotropic hypogonadism require the combined treatment with hCG plus human menopausal gonadotropins to initiate sperm production and fertility (refer to Chapter 24). In those with a selective deficiency of GnRH, such as Kallmann's syndrome, pulsatile GnRH therapy has been shown to stimulate T production and spermatogenesis.

ACKNOWLEDGMENTS

This work was supported by grants DK-45760, DK-43344, and RR-00064 from the National Institute of Health USPHS and Department of Internal Medicine and Pathology funds.

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